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March 14, 1895.

The LORD KELVIN, D.C.L., LL.D., President, in the Chair.

A List of the Presents received was laid on the table, and thanks ordered for them.

The Croonian Lecture was delivered as follows:—

CROONIAN LECTURE.—“On the Nature of Muscular Contraction.” By TH. W. ENGELMANN, Professor of Physiology in the University of Utrecht. Received February 25, 1895.

I beg your kind attention for a few moments to some observations and considerations on the nature of muscular contraction. Besides its general biological interest, the subject may claim a particular interest for the members of this Society, for the venerable institution of these Croonian Lectures is especially devoted to the furtherance of the study of muscular life, and, moreover, the Royal Society has, through its Fellows, from Robert Hooke down to our friend Professor Schäfer, produced numerous researches on muscular structure and action which may be said to belong to the most valuable part of our scientific property.

It will not be my task to recall to your mind all those eminent Fellows of this Society who have helped us to get a clearer insight into this subject, yet I cannot refrain from reminding you of one of these men, who is honoured throughout the whole world as one of

the founders of our present doctrine of muscular structure and action—a man whose name will live on, in my home in Holland, of all countries, associated with the memory of his great brotherly friend, Donders, and whom, to my great grief, I may see here no more—I mean Sir William Bowman.

But a few years ago I had the happiness of seeing him in Utrecht, and of observing how the interest which he took in a province of science in which he had gained his first laurels remained unchanged, even after the lapse of half a century. To behold him among this audience would have been my greatest joy and pride, and his judgment would, in my eyes, have been invaluable. May that which I am now going to say be commended to you at the same time as homage paid to the memory of the discoverer of the sarcous elements and of the waves of contraction.

The subject of my lecture is an inquiry into “The Nature of Muscular Contraction.” Like all vital phenomena, muscular contraction is a most complicated process, composed of mechanical, chemical, thermal, and electrical changes in living matter. Hence it will be our task to become acquainted with these changes as completely and exactly as possible, and to ascertain their causal connection. Our inquiry must not be restricted to one special kind of muscle: it will have to extend to all the different forms, the highest as well as the lowest—muscles in every stage of development, muscles either sound or unsound,—for there can be no doubt but that in all these cases the principle of activity is the same. Nay, it will be necessary to deal even with the other phenomena of so-called contractility, such as protoplasmic and ciliary motion, for all those different types of organic movement, however much they may differ from each other in details, are yet connected by states of gradual transition, so that, to all appearance, one principle of motion, essentially the same, is applicable to all of them.

Only such properties and processes as all contractile structures have in common will consequently have a right to be considered essential to the process of contraction, and only such will be allowed to form the basis of our endeavours to explain muscular motion.

The general mechanical principle on which muscular contraction is based, will apparently be discovered when we shall have ascertained in what way the power of shortening proceeds from the potential chemical energy which disappears upon stimulation of the muscle. There can be no doubt as to the fact, that the potential chemical energy of the component parts of muscular substance is alone the ultimate source of this power, for the existence of any other source cannot be proved.

The quantity of energy which is imparted to the muscle by the

stimulus is too small to be taken into consideration. The early opinion that the power required for contraction was imparted to the muscle through the medium of motor nerves, was refuted by experiments, such as, *e.g.*, those on the persistence of contractility after degeneration of the motor nerves, and on the effects of direct artificial stimulation of the muscles; and it had even been refuted long ere the law of conservation of energy had thrown its light on the mutual connexion between the phenomena of the living organs.

This law teaches that all the actual energy which appears in the muscle in consequence of stimulation, must originate in an *equivalent* quantity of some other form of energy.

Now this form of energy is, in fact, given in the muscular substance liable to physiological combustion. The quantity of the latter is not only theoretically sufficient to produce that actual energy, but it has even been proved experimentally that during contraction the material gives rise to combinations, such as carbonic acid, in the development of which potential chemical energy must have passed into other forms of energy. So far as the phenomena have been examined *quantitatively*, they confirm the conclusion that all muscular force must be derived from chemical energy.

Hence there is no difference about all these points. But with this result we have as yet gained only a basis for the proper solution. As soon as you inquire in what way, by what transformations, does the mechanical force of contraction arise from chemical energy, difficulties and differences of opinion begin to present themselves.

A great many physiologists hold, with Pfüger, Fick, and Chauveau, that muscular force is a direct manifestation of chemical attraction; others, *e.g.*, Solvay, think that it is produced through the medium of electricity; others again, following J. R. Mayer, believe that the muscle is a thermodynamic machine, not unlike our caloric or steam engines.

The Chemiodynamic Hypothesis.—The first hypothesis, according to which contraction of muscle is a *direct* manifestation of chemical attraction—we may call it the chemiodynamic hypothesis—has to assume that the molecules, on the chemical combination of which this contraction is based, are regularly arranged within the contractile substance in such a way that they necessarily approach each other, during that combination, in the direction of the axis of the muscular fibres.

I think that this hypothesis of the identity of chemical attraction and muscular force meets with a fundamental difficulty in the fact that, in a single contraction, only a relatively infinitesimal part of the muscular substance is chemically active. 70 to 80 per cent. of the muscle (and even more) consists of imbibed water, the rest contains substances (albumin, salts, &c.) which, for the greater part, so far as can be proved, are not chemically concerned in the contraction.

This quantitative composition and this minute consumption of the active muscle compel us to assume that relatively only very few molecules of the muscular substance can be considered as sources of energy, and of these again it is generally but a small part that at a certain moment perform their function. How else were it possible for a severed bloodless muscle to continue to carry out, without any perceptible decrease of weight, many thousands of contractions, and how else could a frog's heart, isolated and all but bloodless, beat on for days together, with a nearly constant frequency and but slowly sinking power?

With certain presuppositions we may compute the quantity of matter through the chemical action of which the amount of actual energy, produced at a certain contraction, must have been generated.

If we prevent a muscle from doing external work during the contraction, the whole actual energy will present itself in the shape of heat. When there is but a slight contraction, the muscle of a frog, *e.g.*, will grow warmer by about 0.001° C. Supposing the specific heat of the muscle to be equal to that of water (in fact it is less), we find that to produce a rise of 0.001° C. in temperature a quantity of heat of 0.001 cal. is required for each gram of muscle. No matter whether this quantity of heat results from combustion of carbohydrates, fats, or albuminous matter, it can be but an infinitesimal part of the muscular substance that produced it. If, *e.g.*, as is ordinarily supposed, the combustion of a carbohydrate into CO_2 and H_2O produced that heat, taking the heat of combustion of one gram of carbohydrate to be broadly 4000 cal., no more than a four thousandth part of a milligram will have been consumed in each gram of the muscle. Hence only about a four millionth part of the muscular substance could have been the source of the actual energy, set free by the stimulus, and have served at the same time, according to the above hypothesis, as the seat of direct attraction.

But whatever may be our conception of the size, form, position, and sphere of action of this four millionth part with regard to the rest of the soft, watery mass, only passively moved, I fail to understand how, through *direct chemical attraction*, this one particle should set all those other four million parts, less one, moved, as in fact it does.

We must not forget that we have to deal with enormous changes of form. Muscles of insects are sometimes shortened by local contraction to one twentieth of their length during rest. The myopodia of *Acanthocystis* can be reduced to a fiftieth part of their length by the action of even a weak stimulus; in this case an extremely long, thin fibre is in a moment changed into a short cylinder, about as broad as it is long.

That this can ever be brought about by direct chemical attraction, seeing that but a relatively infinitesimal part of the soft watery sub-

stance of the fibre is the seat of this chemical attraction, seems to me difficult to understand, even if we assume—as I believe we must do—that the *number* of the chemically active molecules is, even in the smallest visible particle, so large that the distances which separate them from each other and from the passively moving molecules lying between them, fall within the limits in which molecular mechanical influence can be exercised.

The adherents of the chemio-dynamic hypothesis have not as yet answered this objection. And since they can give but an unsatisfactory account or no account at all of many other facts (I will refer to some of these facts further on), we may be allowed to cast about for some other explanation.

The Electrodynamic Hypothesis.—Since Galvani's discoveries the electric phenomena of the muscles have frequently been suspected to contain the solution of our problem. And indeed, it is not so very difficult to mention a series of facts which seem to bear out the suggestion that the mechanical work done by the muscle may be created from chemical energy through the medium of electric forces.

There is, in the first place, the fact that muscles, when in action, produce regular electric effects. These effects are indeed the first phenomena we can observe after the stimulation. They seem to begin at the very moment of stimulation, shortly before the contraction; hence they might in so far be the cause of the mechanical process.

Moreover, the value of the electromotive force, as du Bois-Reymond proved, is very high, and in the active particles is probably much higher than the force of the currents we can derive from the surface of the muscle.

Add to this that the economic coefficient of the muscle may attain, just as in the case of electric motors, a considerable proportion. As much as 25 per cent. and more of the potential energy which has been consumed may be transformed into mechanical work.

However, there are weighty objections to this hypothesis also. In the first place, there is the fact that these very same electromotive forces, of equal intensity and direction, appear, under the same influences, not only in the muscles, but also in nerves, glands, and other organs, which do not possess the least contractility. Then there is the important discovery of Biedermann, that the contractility of muscles may be completely neutralized by water or ether vapour, without doing any perceptible harm to the electromotor phenomena.

In the same way the development of the electric organs supplies us with important proofs of the independence of the electric and the mechanical processes. In most cases these organs are developed out of striped muscular fibres. Now, in this process of development, contractility is gradually lost, whereas the power of producing electrical effects attains a yet higher degree of perfection.

The Thermodynamic Hypothesis.—More probable than the chemical and the electrical hypothesis may be deemed a suggestion, first put forward by Jul. Rob. Mayer, though in an untenable form, according to which the muscle is a thermodynamic machine. Physiologists, however, generally object that this view is not compatible with the second law of the theory of heat, for we cannot expect differences in temperature in the muscle so great as this law requires they should be.

Now I think that, on the contrary, we must assume exceedingly large differences of temperature in the stimulated muscle. What holds good of the whole body holds good of the muscle also; the temperature, measured with our instruments, is but an arithmetical average, "comprising an infinite number of different temperatures, pertaining to an infinite number of different points" (Pflüger).

From the fact that at the contraction an infinitesimal part only of the muscular mass is chemically active, we infer that the temperature of these particles must, at the moment of combustion, be an uncommonly high one. Great as the specific heat of muscular substance is, it would otherwise be impossible to account for a rise in the temperature of the whole mass even of 0.001°C . only. Without any exaggeration we may assume that the temperature of the chemically active particles may, at the moment of combination, exceed the average muscular temperature by hundreds of degrees.

Since each thermogenic particle is surrounded by a relatively enormous cool mass, conducting heat and diathermanous, the principal condition for the transformation of heat into mechanical work has been satisfied, and, on account of the enormous differences in temperature which we have to assume, in such a high degree, that even an economic coefficient of 30 per cent., nay, 50 per cent., and even more, seems to be theoretically possible.

Supposing we have to deal with a Carnot's cycle, the theoretical maximum Q_0 of the mechanical effect is $Q_0 = Q \frac{T_1 - T_2}{T_1}$, where Q stands for the whole quantity of heat, which from the absolute temperature T_1 is sinking down as far as T_2 . Taking $T_2 = 273^{\circ} + 37^{\circ} = 310^{\circ}$, the mechanical effect might at $T_1 = 410^{\circ}$ amount to 25 per cent., when the temperature of the active particles would consequently exceed the average temperature of the normal muscle by 100°C . only.

The objection that these high temperatures must necessarily destroy the life of the muscle, since the latter becomes rigid and dies even at 50°C ., is, for the same reasons, of small value only. For it is ever an infinitesimal part only of the muscular mass that is exposed to these high temperatures. At a small distance from these furnaces of heat the temperature must have fallen so low as to be

harmless. The muscle will no more be destroyed by stimulation than a steamship will be destroyed by heating the furnaces. The material of combustion only will be destroyed; the vessel as a whole remains unharmed.

However likely it may thus seem that nature should avail herself of these favourable terms on which mechanical work may result from muscular heat, we have had up to the present time no direct proof that this is actually the case, nor do we know in what way it takes place, if in any. But I venture to think that the proof can now be given, inasmuch as it is possible to demonstrate how, through the medium of peculiar arrangements of the material of the muscle, a transformation of chemical energy into mechanical work by means of heat not only can, but actually must, be brought about.*

Muscular Structure in relation to Contractility.

The Fibrils are the Seat of the Shortening Power.—For this we need firstly to pay attention to the peculiarities of the microscopical structure of muscle. All muscular fibres of all animals are composed chiefly of two parts: extremely thin, long, albuminous fibrils, and an interfibrillar plasmatic substance, the so-called sarcoplasm. The quantitative relations of both vary, but the fibrils always occur in great number, forming very often the greatest part of the whole mass of the muscle. They always run parallel to each other throughout the length of the fibres.

This fibrillar structure is also presented by all the other formed contractile substances, such as the myonemata of Infusoria and of other Protozoa, the cilia and vibrating membranes of cells, the tails of spermatozoa, nay even, at least, when not in a state of contraction, by the amoeboid protoplasm of *Pelomyxa*, *Myxomycetes*, and other forms.

Direct microscopical observation during life teaches us that the fibrils, and not the sarcoplasm, are the seat of the shortening power. The fibrils in a state of relaxation are long and thin, and often run in winding curves, but grow short, thick, and straight, in consequence of stimulation. The sarcoplasm passively follows their movements. Moreover, completely isolated fibrils can shorten.

The Fibrils are Contractile because they contain Doubly Refractive Particles.—Thus the question arises: can there be demonstrated in the fibrils arrangements such that by means of them contractile force may originate in a thermodynamic mode?

* The empirical foundations of the views developed in this lecture will be found in "Versuche über Aenderungen der Form und der elastischen Kräfte doppelbrechender Gewebelemente unter chemischen und thermischen Einflüssen," in the Appendix of my Memoir: 'Ueber den Ursprung der Muskelkraft' (2te Auflage. Leipzig. 1893. Pp. 54—80), and in the literature cited in the same paper.

Light—*lux optimum reagens*, as Buys Ballot said—solves this question for us. If we examine the optic properties of contractile fibrils, with the aid of the polarising microscope, we find that all of them are double-refractive, with one optical axis parallel to the direction of contraction. This property, long ago discovered by Boeck in the striated muscles of the higher animals, has now been proved to appertain to the muscular fibres of all the animals examined for that end, to the contractile fibrils of Protozoa, *e.g.*, to the muscle of the stalk and the myonemata in the subcuticular layer of Vorticella, to all kinds of ciliary apparatus, and in many cases to contractile protoplasm also.

This general occurrence of double-refracting power is the more indicative of relations to contractility, since non-contractile cells, as a rule, lack double refraction, even where we meet with a fibrillar structure, as in the axis-cylinder of a nerve-fibre.

Our conjecture gains, I believe, a very high degree of probability by the following series of observations, which are the more convincing since they relate to quite different categories of phenomena, independent of each other.

In the first place, there is the fact that contractility and double refraction in the course of ontogenesis always appear at the same time, *e.g.*, in the heart of the chick on the second day of incubation; in the muscles of the trunk and skin on the fifth or sixth day; in the muscles of the tails of tadpoles when the length of their body is 3 to 4 mm.; in the muscles of the stalk of Vorticella, and in cilia so soon as these organs become visible.

Other evidence seems to me to be afforded by the behaviour of the striated muscles. Here the fibrils consist of the doubly-refractive sarcous elements and the singly-refractive material which joins these, the two alternating regularly. The two are wholly different as regards their optical, mechanical, and chemical properties; and these properties, moreover, during contraction, change in an opposite way. Hence the functions of the two must be different. And since the changes of form, volume, &c., of the doubly-refractive parts during contraction prove that in each case these parts must be the seat of contractile power, the singly-refractive junctions will most probably have another function. We will come back to these changes further on.

A third evidence is afforded by the observation that the specific force of contraction in different muscles is, in general, greater, the better developed the power of double refraction, comparison, of course, in each case being made with parts of the same thickness.

In the development of the pseudo-electric organs of *Raja* out of striated muscular fibres, one of the signs of the incipient change of structure and function is the vanishing of double refraction in the

sarcous elements. In an early stage of development this vanishing is, with *Raja clavata*, the very first and the only sign that the fibre is about to be transformed from a contractile into an electric organ.*

But particularly significant seems to me to be the behaviour of the obliquely striated muscles of Molluscs and other Invertebrata. Here the doubly refractive fibrils do not run parallel to the axis of the fibre, but describe spiral lines round it; and during a contraction the steepness of the curves decreases, so that the angle formed by the longitudinal axis of the fibril and the longitudinal axis of the fibre may increase from 5° in the relaxed state to 60° , and even more, in a state of powerful contraction. But the optic axis of the fibril, instead of assuming, in this case, a more oblique position also, as might be expected on morphological grounds, remains parallel to the longitudinal axis of the fibre, and consequently to the direction of shortening of the fibre. Hence it is not the morphological axis of the fibrils, but the optical axis of their doubly refractive constituents, which coincides with the direction of the contracting force.

Contractility a General Property of Doubly Refractive Bodies.—More than a score of years ago I pointed out the fact that even non-muscular elements, elements not possessing irritability in the physiological sense of the word, nay, even lifeless, unorganised elements which are doubly refractive and uniaxial, may, under certain influences, contract in the direction of the optical axis, all thickening at one time, and contracting with a force and quickness and to an extent rivalling that of muscles, if not surpassing it. Instances of this are the fibrils of connective tissue, of the tendons, and of the cornea and others. The same contractile power was found by von Ebner in a great many other doubly refractive histological elements, nay, even in substances capable of imbibition and thereby made doubly refractive, *e.g.*, dried colloid membranes; and finally by Hermann in fibrils of fibrin.

I have in this way shown that singly refractive, or only feebly doubly refractive histological elements, such as fibres of elastic tissue, in the same way as caoutchouc, obtain the power, when made doubly refractive by extension, of contracting under certain influences, and further that the force of shortening will generally be greater in proportion to the amount of the double refraction thus artificially produced.

Since, according to Mitscherlich's discovery, similar changes of form may be observed in doubly refractive crystals, we have apparently to deal with a property pertaining to all doubly refractive bodies as such.

Heat as a General Cause of Contraction of Doubly Refractive Elements.—Now, the influence which in all these cases is able to evoke the

* Th. W. E., "Die Blätterschicht der electrischen Organe von *Raja* in ihren genetischen Beziehungen," &c., 'Pflüger's Archiv,' Bd. 57, 1894, p. 149.

mechanical energy of shortening is *elevation of temperature*. Cooling has the opposite effect.

Particularly instructive is the thermal contraction of fibrillar connective tissue, on account of its similarity to muscular movement, even with regard to details. This tissue, like muscle, consists of doubly refractive fibrils and of an inter-fibrillar singly refractive isotropic substance. The fibrils have about the same dimensions as muscular fibrils, and, for the rest, show, in their optical and mechanical behaviour under various influences, a great likeness to muscular fibrils, especially to the doubly-refractive sarcoous elements.

In tendons and many membranes the fibrils, as well as those of most muscles, are arranged into bundles, all, or nearly all, parallel to each other. For this reason such objects are extremely well fitted for a closer examination of the phenomena of movement. The most suitable material I know is furnished by the catgut string of a violin, which consists chiefly of such bundles, running in steep spiral lines round the longitudinal axis of the string. Such a string is distinguished from the greater number of naturally occurring objects by its very regular cylindrical shape and its elasticity. On these properties is based its suitability for musical purposes, especially for the so-called "perfect fifth" ("Quintenreinheit").

The Muscle-Model.—With the aid of such a string we can compose a model which in a simple way explains how in the muscle mechanical energy of contraction may result from heat without any perceptible rise of the average temperature of the muscle.

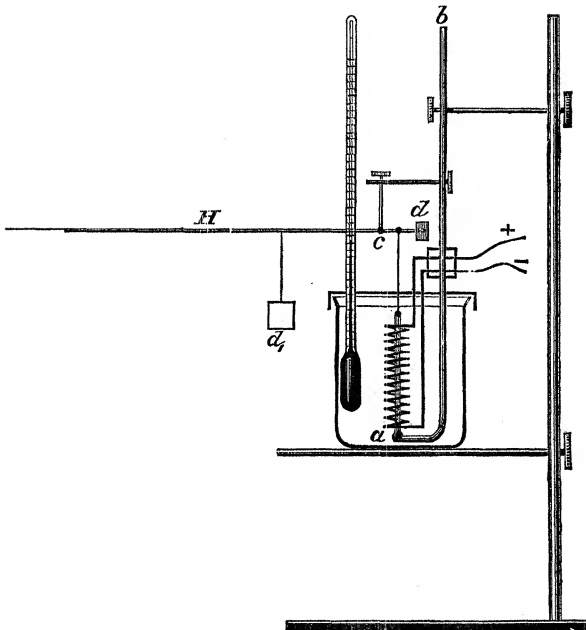
The following sketch (fig. 1) presents this *model of the muscle* diagrammatically simplified:—

A piece of an *E* string of a violin, about 5 cm. long and previously swollen in water, is fastened to the end, *a*, of the short rigid arm of a steel rod, *ab*, while the upper end of the string is fixed on the shorter arm of the lever, *H*, turning round the horizontal axis, *c*.

To this string different tensions may be imparted by weights (*d*, *d*₁), or springs, acting upon the lever, and since the point of application of the string may be changed at will, its contraction, with all the conditions of isometry, isotony, and auxotony may be examined.

Round the string, but without touching it, runs for a length of about 20 mm., and in about twenty curves, a spiral of thin platinum wire. Its ends may be connected by means of two binding-screws of the ebonite or ivory piece, *f*, with the two wires coming from the poles of a Grove or Bunsen battery of three or more cells. The rod, *ab*, bearing lever, string, and spiral wire, is placed in a glass of about 50 c.c. content, filled with water of about 55—60° C., and closed at the top by an ebonite lid. Through an aperture in the lid, a thermometer is placed in the water in such a position that it will remain at a distance of about 1 cm. from the spiral wire.

FIG. 1.



The string is now observed for some minutes at a tension of 25 or 50 grammes, and at a constant temperature, until no further change in the position of the lever can be discerned. If we now close for some seconds the circuit of the battery through the spiral, *the lever rises. Upon opening the circuit, it falls. The thermometer in the glass indicates a hardly perceptible rise in temperature, or no rise at all.*

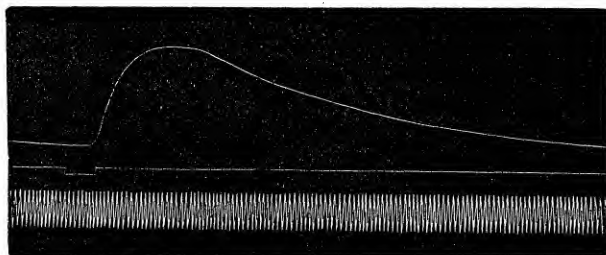
We see the doubly-refractive string of our model corresponds with the doubly-refractive muscular particle, which we suppose to be the seat of the force of contraction, and therefore may be called "*inotagma*;" the water in the glass represents the watery isotropic substance round the inotagma, doing duty as refrigerant; the spiral wire supplies the place of the chemically active *thermogenic* molecules; the closure of the galvanic circuit corresponds with the process of the stimulation of the muscular element.

The experiment may be simplified by heating in the air a string previously made to swell by being dipped in hot water and then soaked in concentrated glycerine. The movements will then take place more quickly on account of the quicker heating and cooling. Moreover, the experiment may be repeated almost as often as one likes. If we fasten to the lever a little metallic hook, which when

sinking closes the circuit of the spiral by dipping in mercury, and breaks it again when rising, contraction and relaxation of the string will alternate regularly for hours, just as with a beating heart.

The movements may be inscribed on a rotating cylinder. We then obtain curves of the same character as contraction-curves of muscles (fig. 2).

FIG. 2.



Such a *chordogram* presents, like a myogram, three periods, viz.:—

1. A period of latent energy, the duration of which, just as with the muscle, decreases with the increasing energy of the stimulus (*i.e.*, with the intensity and duration of the electric current), with rising temperature and with decreasing load.

2. A period of augmenting energy, in which contraction takes place with a rapidity, first increasing, afterwards diminishing, the contraction being, within certain limits, more rapid and larger in extent the stronger the stimulation.

3. A period of declining energy, in which the string relaxes with a gradually decreasing rapidity.

Further Comparative Researches on the Thermal Contraction of Lifeless Doubly Refractive Bodies and the Physiological Contraction of Muscle.—The points of resemblance between our model and a muscle extend much further yet, and amongst other to peculiarities which seem to bear important testimony to the identity of the mechanical process in the two cases.

Such a resemblance I find, in the first place, in the fact that the strength of the *shortening power*, developed by a certain stimulus, increases with the load within certain limits. Both muscle and string present the paradoxical phenomenon that, under a stimulus of equal energy, heavier weights may be lifted higher than lighter ones.

Adolf Fick first detected this surprising fact in the muscles of *Anodonta*; and Rudolf Heidenhain, almost at the same time, observed it in the striated muscle of Vertebrata. It has been generally confirmed, and seems to hold good for all kinds of muscles.

Neither the chemical nor the electrical hypothesis of the origin of

muscular force can give a sufficient explanation of this fact. On the basis of our theory, on the contrary, it can be predicted, because every influence which augments the doubly-refractive power must raise the power of contraction.

Now, von Ebner has proved experimentally that the doubly refractive power of tendons and also, between certain limits, of muscles, increases with the load. The same is the case with fibres of elastic tissue and with caoutchouc, and here also the contractile power increases with the load.

The differences of force which depend on the load are by no means insignificant. According to Fick the lifting heights for 5, 8, and 10 gr. were, with a muscle of *Anodonta*, related to each other as 8.3 : 10 : 16.3. With *E* strings, swollen in hot water, I obtained, when heating them from 20° to 80° C., at an initial load of 5 gr., a contractile power of but 55 gr.; at a load of 50 gr. one of 80 gr.; and at a load of 90 gr. one of about 120 gr.

For *E* strings swollen in lactic acid of 0.25 per cent. the rates of power, corresponding with the initial tensions of 5, 90, and 125 gr., amounted to about 100, 125, and 154 gr. A strip of elastic tissue, 2 mm. thick, heated at 80° C., gave for an initial tension of 10 gr., at which the double refraction of fibres is just beginning to be perceptible, a power of but 61 gr., for 100 gr. one of 162 gr., for 185 gr. of initial tension, at which double refraction is very strong, one of 238 gr. A strip of vulcanised caoutchouc, 2 mm. thick, which, unloaded and hence singly refractive, did not, even when heated to 100° C., tend at all to become shorter, developed with an initial load of 90 gr., put on at 20° C., a contractile power of 110 gr. at a temperature of 80° C., while at the same time a strong power of double refraction had been acquired by it.

Now, it is true, that Heidenhain has found that—at least in the stimulated *striated* muscles—not only mechanical energy but also the development of heat and the formation of lactic acid increase together with initial tension. But, according to his experiments, mechanical energy increases much more rapidly than does the production of heat. This difference at least might be explained by the influence of extension on the doubly-refractive power. An influence of extension on chemical action may very well be associated with the influence on double refraction, as a consequence of the changes in the local arrangement of the thermogenic particles which are produced by the extension. Such changes must be effected to a considerable degree, even when the shortening of the muscle is prevented by resistance (isometric contraction of Fick), and especially in the case of striated muscles, to which Heidenhain's statements refer. For not only fibrils, interfibrillar substance, and sarcolemma, but also the singly and the doubly-refractive portions of the fibrils differ much

in elasticity. It would be very strange if these shiftings did not manifest themselves also in changes of the chemical processes, and if these changes were not conformable to the purpose.

Connected with the point we have just discussed is another fact, viz., that the amount of shortening produced in our model by means of a given rise of temperature, is the smaller the more the string has already contracted. The maximum of force is, at all events, displayed when the extension of the string is brought about by the whole load being applied at once at the very beginning of the heating, not after the string has already contracted with a smaller load.

The very same thing, as Schwann's experiments showed many years ago, holds good of muscle. On the hypothesis of chemical attraction we should decidedly expect the reverse: viz., increase of force with an increasing mutual approach of the combining molecules; so also in the same way on every hypothesis which pronounces contraction to be caused by attractive powers increasing in inverse ratio to the square of the distance.

In the fact discovered by Schwann, Johannes Müller thought he had found a refutation of the old electro-dynamic hypothesis of Prévost and Dumas, as well as a valid reason for assuming a fundamental relation between the vital power of contraction and physical elasticity.

However, as Hermann has observed, we might in this case get over the difficulty by supposing that between or in the length of the parts attracting each other, there are elastic layers opposing that attraction with increasing force. It is evident that our view of the matter does not require such an auxiliary hypothesis, because, following Eduard Weber, we regard muscular contraction as only a special case of elastic shortening.

A closer experimental comparison of the changes undergone, on the one hand, by the elasticity of our string during thermal shortening, and, on the other, by muscular elasticity during physiological contraction, will teach us that, in each case, those changes are of exactly the same kind.

As regards striated muscles, it was Eduard Weber who, by his classic researches, established that their extensibility increases during contraction. The same is now proved to hold good of strings and other organic doubly-refractive substances during thermal shortening.

The curve of lengthening of all these objects inclines more sharply towards the abscissa of the loads the higher the temperature. Both curves converge and may finally even cross, *i.e.*, a certain load being exceeded we do not get contraction of our string, but lengthening as the effect of heating.

This circumstance explains the fact, sometimes observed by E. Weber, that living, tired, heavily-loaded frogs' muscles, lengthen

instead of shorten as a result of electric stimulation. Considered from other theoretical points of view, this observation seems so paradoxical that its very validity has been questioned by some physiologists; but in the face of the direct and exact measurements of so scrupulous an observer and inquirer as Eduard Weber, we have no right to do this. Moreover, Charles Richet and de Varigny have confirmed the observation with different kinds of muscles of Invertebrata. According to our view of the origin of muscular force the fact is not paradoxical at all, but might be foreseen.

The decrease of the shortening power and the increase of extensibility with increasing thermal contraction is, in the case of our lifeless doubly-refractive objects, accompanied by a decrease in the power of double refraction. According to von Ebner's careful measurements, confirmed by Alex. Rollett, the same thing is the case with muscles during vital contraction. We may consider this fact, too, as an important proof of the fundamental resemblance between the process of contraction in our model and in the muscle, and at the same time as a further evidence of the existence of a causal relation between double refraction and contractility in general. But it is the physicist's task, and not the physiologist's, to penetrate further into the relations between optic and elastic properties. The physiologist may deem his purpose attained when he succeeds in tracing a certain vital phenomenon back to processes which may also be observed in lifeless bodies.

However, though we should, perhaps, be inclined to infer from the foregoing that we have successfully acquitted ourselves of this task with regard to muscular contraction, we will be careful not to overlook the numerous important respects in which a muscle as a *living* body, that is, one subjected to constant chemical transformation, differs from our lifeless strings. The study of these differences is most instructive, since it throws a new light on a series of processes nearly allied to contraction, especially on the phenomena of *rigor mortis* and *tonus* of muscle.

But before entering into this we shall first have to meet another important objection to our views. It is based upon the absolute amount of muscular force. This amount may, as you know, be very high. Human muscles at the strongest tetanic contraction can shorten with a force of about 10 kilogrammes to 1 sq. cm. of transverse section. Now such a force must, according to our view, be produced by a very small part only of the transverse section of the muscle.

With a maximal tetanus, it is true, the temperature of the whole muscle does rise 1° C. or more. Hence there are, perhaps, 1,000 times more particles chemically active than with a moderate simple contraction, where the temperature rises 0.001° C. only. Consequently,

during such a tetanus, a much greater part of the muscular substance—perhaps 1,000 times as much—will be heated to such a degree as is required for an obvious contraction of the inotagmata. But even in this case the greater part of the whole substance will be only moved passively.

This holds good also, though in a less degree, of the single fibrils or of the single sarcous elements, which, on account of their containing doubly refractive inotagmata, we believe to be the sole producers of shortening power. For it is beyond question that the sarcous elements *in toto* are not subjected, even during the strongest tetanus, to a temperature so high as is required by our hypothesis. Hence the specific force of contraction of the individual doubly-refractive elements must be comparatively much greater. We cannot properly calculate *how much* greater the absolute force of a muscle would be if the transverse section consisted of nothing but contractile inotagmata, we can only assume that it would, in general, be many times as great.

Can such very important mechanical powers as we are obliged to assume in the inotagmata be developed through the thermal contraction of doubly-refractive bodies? Do we not, as Fick says, go beyond the bounds of legitimate analogy in making such a supposition?

Of course nothing but the measurement of the forces developed by lifeless doubly-refractive bodies under thermal contraction will decide this question. I have made many of these measurements on various objects, and I think the results furnish us with a refutation of the objection. Strings, moist but not yet contracted through lying in water, with a diameter of 0.7 mm., and loaded with 1 kilogramme, lifted up the weight in a perceptible degree when rapidly heated up to 130° C.; that is to say, they exerted a force about twenty times at least as great as the maximum force of a human muscle of the same thickness. This is all the more striking, since in strings also it is not the whole transverse section, but the sum of the sections of the fibrillæ, and even a part of every section only, which is the seat of the power of shortening.

Still greater forces may be exerted by strips of caoutchouc rendered in a high degree doubly refractive by strong extension. Even merely heating from 20° to 40° C. produced results sixty times as great as the maximum afforded by human muscles of the same transverse section.

Hence we may sufficiently account for the greatest display of force of which muscle is capable, without having to attribute to the inotagmata higher elastic forces than we observe in highly extended threads of caoutchouc of the same thickness, nay, without even having to assume temperatures reaching the degree necessary for the coagulation of albumin.

Influence of Heat on the Dead Muscle Fibres.—It is a pity that we

are not able to subject the isolated doubly-refractive parts of the muscle in an unimpaired condition to the influence of heat. Together with the elevation of temperature there occur changes in the chemical processes, and therewith in the material composition and mechanical properties of the whole muscle substance, which complicate the changes dependent only on the heating of the doubly-refractive particles, or even prevent our clearly recognising them.

We may, it is true, exclude these chemical influences by previously killing the muscles by means of alcohol or some other medium, the action of which preserves the finer structure of the non-contracted muscle, and above all the double refraction. But in this case, too, the mechanical properties of the fibrils, as well as of the sarcoplasm, change so considerably that the explanation of the phenomena becomes very difficult. A great part of the soft muscular substance becomes solid by coagulation or precipitation, and these solid parts will act in opposition to a thermal shortening, nay, perhaps compensate it, in consequence of their own expansion through heat. Moreover, the phenomena are rendered complicated by the thermal changes of other elements of the muscular tissue, such as connective fibrils, blood-vessels and nerves.

The results, however, agree very well with the hypothesis that even in a dead muscle the doubly-refractive particles tend to contract when heated to a certain degree, and to lengthen again when cooled. The degree of heat at which quite dead, lightly loaded frogs' muscles begin to shorten, does not lie much higher than those sufficient to produce rigor, mostly below or near to 60° C. Contraction increases with the temperature, occasionally amounting to 20 per cent. of the initial length.

Very important contractions of the sarcous elements—to the half of the length and more—are shown by the microscope in the striated muscles of insects, when these are very rapidly heated to 55°, or higher. The singly-refractive layers do not contract, or at least to a much less degree. However, we will not attach too much importance to these facts, because the conditions are very complicated.

Tetanus and Rigor by Heat.—Living muscles, when being *gradually* heated, are, as you know, thrown into tetanus so soon as the temperature has attained the height of a little below 50° C. This so-called *tetanus of heat* passes by prolonged heating into the lasting contraction of *rigor*, accompanied by definitive loss of irritability.

This contraction through heat agrees in so many points with physiological contraction, especially with physiological tetanus, that it was long held to be the last manifestation of muscular life. Such points of resemblance are, *e.g.*, the amount and the force of shortening, which in both cases are at least of the same order, and the increased production of heat, of carbonic acid, and of a fixed acid.

No doubt in this case a very important and general rise of temperature of the contractile particles will take place so soon as rigidity begins to announce itself. Consequently, according to our hypothesis, we must expect a strong and general contraction of the inotagmata.

That the force, with which the muscle as a whole will shorten, is not quite so great as with physiological tetanus, is sufficiently explained by the fact that the inotagmata do not contract simultaneously, and by the increase of internal resistance which occurs, due to coagulation and precipitation in the muscle plasma during the development of rigidity by heat. The latter circumstance seems to explain, too, why the rigid muscle does not perceptibly, or only very little, lengthen upon cooling.

Turgescence by Imbibition as a General Cause of Contraction of Doubly-refractive Organised Elements.—On a closer examination, however, we find that matters are still more complicated, and likewise that there is still an important circumstance which, besides the rise of temperature of inotagmata, may act as a cause of contraction, even of permanent contraction. This circumstance, the fundamental importance of which to muscular contraction was disclosed a score of years ago by a rigorous microscopical examination of the processes taking place in the muscle fibres during contraction, is the *turgescence of the doubly-refractive elements by the imbibition of watery liquids*.

All histological elements possessing doubly-refractive power tend, even at an ordinary low temperature, to contract in the direction of the optical axis when their volume is enlarged by the imbibition of a watery fluid, and to lengthen when their volume diminishes by loss of liquid. The extent, power, and rapidity of the changes of form depend on the nature and on the dimensions of the turgescient object, and on the nature and quantity of the imbibed liquid.

For the examination of these relations our violin strings again yield fit material. A long series of measurements has now shown that there is a very close resemblance between contraction by imbibition and thermal and physiological contraction. I may mention the marked extent of the shortening, the high value of the force of contraction, its increase with the initial tension and its decrease with increasing shortening, the increase of extensibility, the decline of refractive power and of doubly-refractive property. The resemblance is by no means exclusively of a qualitative, but also of a quantitative kind.

A change of form generally takes place when the composition of the imbibed liquid changes, and it is of great importance to our question that even the slightest changes of composition can cause marked contractions and great mechanical effects.

Unloaded *E* strings, e.g., contract in pure water to nine-tenths, and in water which contains 0.25 per cent. only of lactic acid to three-

fifths of the initial length. At 15° C. they exert, in the first case, forces of about 80 gr., in the second of about 110 gr. With initial tensions of 105, 335, and 450 gr., forces of 226, 365, and 496 gr. respectively were produced by swelling in distilled water at 15° C.; and by imbibing a 0.25 per cent. solution of lactic acid at initial tensions of 5, 215, and 425 gr. forces were exerted of 115, 350, and 490 gr. respectively, *i.e.*, forces very much higher than a muscle of the same thickness can produce during tetanus. Even in a watery solution of only 0.1 per cent. of lactic acid, the strings contract to about 70 per cent., as also in highly-diluted acetic and hydrochloric acid or in potash.

Upon neutralisation or dilution the old length and volume return. The doubly-refractive fibrils, or the sarcous elements of muscles, contract considerably, also under the same conditions, swelling at the same time; this is the case even with muscles which have been killed in alcohol. In such instances I measured in the striated fibres of insects, distinguished by especially long sarcous elements, shortenings to 50 per cent. and more.

Since, according to many inquirers, lactic acid is formed during the rigor of striated muscles, and at all events the reaction of the muscular plasma grows acid, the doubly-refractive elements must necessarily swell more and tend to shorten, and this contraction will remain until the acid has been neutralised or removed by diffusion.

Similar results will be obtained in other cases of rigor characterised by shortening and by the production of much acid, such as the ordinary rigor mortis, the rigor produced by distilled water, the rigor which is caused by excessive stimulation, &c. Nay, in a bloodless muscle even a physiological stimulation, when sufficiently strong and long, may be expected to produce a lasting shortening, on account of the gradually increasing acidity. Indeed, the well-known incomplete relaxation of such muscles seems to me to be a symptom of this *chemical contraction*, as it may be called, in contrast with the *thermal*.

In a muscle in which the blood stream is maintained this will not so easily take place, not even under a strong and prolonged stimulation, because the acid is immediately neutralised or removed through diffusion. Even in the isolated, bloodless muscle the acid, which is produced by stimulation, may, in the beginning at least, be rendered harmless through the very large quantity of non-acid fluid imbibed by the muscle. Consequently we must expect in these cases an immediate and complete relaxation after contraction. The facts agree absolutely with these suppositions.

It is, perhaps, not unnecessary to remark that all these observations would also hold good if the material affecting the turgescence were not lactic acid, but another substance arising during the chemical action in the muscle, *e.g.*, water.

The different parts played by "Thermal" and by "Chemical" Contraction in the different kinds of muscular contraction.—But now the question may be raised: Is not physiological contraction due to turgescence by imbibition solely? Do not we find a sufficient explanation of all kinds of contraction in the change of the conditions of imbibition, a change which must necessarily result from the chemical action caused by the stimulus?

We have all the more reason to put this question, since we can prove, that in the physiological contraction of striated muscle-fibres the doubly-refractive layers swell at the cost of the watery isotropic layers. The microscopical examination of active living muscles and of fixed waves of contraction has proved this fact beyond all question, however much the opinions of different observers may diverge on other points. The swelling would, moreover, account for the slight decrease of muscular volume observed in strong tetanic contraction. For, according to the experiments of Quincke, the imbibition of water by organised bodies generally leads to a slight condensation.* By this condensation further heat is developed, and this heat might, by raising the temperature of the doubly-refractive elements, be partially transformed into mechanical energy, and in this way contribute to the production of muscular force.

Yet I cannot consider this explanation as sufficient for all the facts. The same argument which in our eyes seems to dispose of the hypothesis of the identity of chemical attraction and muscular force, viz., the infinitesimally small quantity of substance which is chemically active during a simple contraction, seems to me to present a fundamental difficulty here also. It is hard to understand how through a change in the material composition, effected at one infinitesimal point within a soft watery substance, the whole mass should shorten and thicken, *unless there proceeds from the centre of chemical activity a considerable amount of kinetic energy throughout the substance.*

The microscopic appearances which prove the turgescence of the doubly-refractive refringent elements during a contraction, do not exclude a direct thermo-dynamical effect. For the almost complete identity in the changes of form, and of optical and mechanical properties, which the doubly refractive constituents of all histological elements undergo during chemical and thermal contraction, seems to bear out the hypothesis, that in the thermal shortening of doubly-refractive elements, through the imbibition of watery fluid, we get a shifting of solid and liquid substances analogous to that of turgescence. In most of the microscopical phenomena, especially the so-called fixed contraction waves, we have, moreover, to do with a high degree of tetanic contraction, or even with rigor, in

* In the thermal contraction of tendons and strings I have not yet been able to convince myself of a decrease in volume.

which, on account of the greatly-increased chemical action, a chemically-caused turgescence may be accompanied to a considerable extent by thermal contraction.

Moreover, it is doubtful if we have in this case to deal with a phenomenon common to all kinds of muscular fibres. Most probably the mutual relations of the two processes differ with different kinds of muscle.

Hence, we may conclude that chemical contraction by turgescence of the inotagmata is most likely a constant concomitant of the thermal contraction of living muscle, but that compared with the latter, in a single contraction, at least of striated fibres, the former is of little or no consequence as regards the shortening effect.

Chemiotonus and Thermotonus.—Both processes will probably also take part in varying proportion in the *tonus* of muscle, which in some cases will approach more to pure *chemiotonus*, in others more to pure *thermotonus*. Experimental researches in this direction are wanted.

Causes of the Relaxation of Muscle. Theoretical Considerations. Conclusion.—With regard to the *relaxation* of muscle, according to our theory this must be caused either by cooling, or by the withdrawal of water from the doubly-refractive particles. Indeed, we have found that doubly-refractive histological elements in general, even if they be lifeless, like our violin strings, lengthen again upon cooling after they have been contracted by heat, and that they lengthen upon neutralisation or diffusion, after they have been contracted by imbibition at an ordinary temperature.

In a normal relaxation the muscle seems to return completely to its initial state. Of course its store of energy has diminished in proportion to the quantity of mechanical work and heat which has proceeded from it, but, on account of the relatively infinitesimal quantity of substance which is thereby consumed, this return will necessarily seem to be complete even in the case of an isolated muscle.

If we analyse the phenomena of relaxation more exactly, we shall light on several possibilities, the discussion of which would be very interesting with regard to the theory of muscle-life. I shall restrict myself to the phenomena of the relaxation following on *thermal* contraction.

Here, in the first place, we might conceive that the doubly-refractive inotagmata are destroyed in the thermal shortening, so that each of them performs its function once only. The lengthening of the muscular fibrils would then probably be caused solely by the elastic powers of the parts passively extended or compressed by the shortening of the inotagmata. Upon a fresh stimulation, other inotagmata would, in consequence of the combustion of other thermogenic molecules, become active, perish, &c. Through the activity of the formative matter of the living muscle-fibre, the place of the lost

inotagmata would be continually or periodically filled by others, probably through the same process of organic crystallisation by which during ontogenesis the doubly-refracting particles in the muscle are produced and arranged.

Against this hypothesis, however, or at least against its general validity, various objections may be put forward. I will mention but two of the most important of them.

There seems to be no doubt but that the doubly-refractive particles of the muscle consist of an albuminous substance, and that they together make up a sensible part of the whole albumin of the muscle-fibrils. In that case it would be most improbable that a great increase of muscular work should not at all, or only very slightly, increase the elimination of nitrogen. To account for this, we should have to recur to an auxiliary hypothesis, and assume either that the nitrogenous remainder of the destroyed inotagma is retained within the body—perhaps in the muscle—for purposes of anabolism, or, which is indeed most improbable, that other organs saved just as much albumin as was decomposed above the normal quantity during the contraction of the muscles.

A second objection consists in the fact that after heating or tetanising muscles until they are rigid, the doubly-refractive power of the sarcous elements will be found still very great.

The other possibility is that the inotagmata may be preserved, and consequently on cooling may return to their former state, and therefore will do work by shortening as often as we choose. In this case muscle would not only seem to offer, but would in fact offer a most striking resemblance to a thermodynamic machine, the solid particles of the framework of which are not destroyed through the chemical process producing the actual energy. No more than such a machine would the muscle require a perpetual renewal of its framework for the continuation of its activity; it would only want a periodic supply of fresh combustible material.

This representation, as you see, will sufficiently account for the fact, which would otherwise remain surprising, that muscular work has such a small influence on the elimination of nitrogen. The facts of microscopic observation also agree with it.

But a further discussion of the two possibilities would lead us too far. The purpose of this lecture was not to give a complete account of all the phenomena of muscular activity. I have wished chiefly to draw your attention to a series of facts which I hold to be of great importance for a deeper insight into the essence of muscular contractility, in so far as they prove the existence of certain material dispositions and processes (admitting of closer experimental examination), by means of which mechanical work may be generated in the muscle by chemical energy.

As with all problems of natural philosophy we must forego the complete solution, and content ourselves with approximations to truth, so now we will refrain from calling out with Archimedes, *εὑρηκα*, but rather be mindful of the words of the apostle :

οὐχ ὅτι ἤδη ἔλαβον, διόκω δὲ εἰ καὶ καταλάβω.

Presents, March 14, 1895.

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FIG. 2.

